CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 20-972

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-972	**REVIEWER:** Vanitha J. Sekar, Ph.D.
DRUG: Efavirenz (Sustiva®)	**TEAM LEADER:** Kellie Reynolds, Pharm.D.
FORMULATION(S): 50, 100, 200 mg capsules	**SUBMISSION DATE:** June 11, Sept 17, 1998 (see below for submissions to the IND)
APPLICANT: Dupont	**DRAFT REVIEW:** 9/2/98,9/28/98,10/2/98,10/7/98
LOGGED IN: 6/16/98	**FINAL REVIEW:** 10/7/98

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BACKGROUND

This review contains a summary of the studies submitted to the Human Pharmacokinetics and Bioavailability section in support of NDA 20-972. Individual study reports, including data, are on file in HFD-880 (Division of Pharmaceutical Evaluation III). The applicant is seeking approval of efavirenz (Sustiva®) capsules. Efavirenz is a HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor. Efavirenz, in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection at a dose of 600 mg once a day. The applicant is proposing to market efavirenz as 50 mg, 100 mg, or 200 mg capsules for oral administration.

Clinical efficacy data from nine Phase II/III studies and one pediatric study have been submitted to support the accelerated approval of efavirenz. The Phase II studies include DMP 266-003, DMP 266-006 and DMP 266-005 which were deigned to test the efficacy and safety of efavirenz in combination with a protease inhibitor (indinavir, in DMP 266-003), or in combination with dual NRTIs (ZDV and 3TC, in studies DMP 266-004 and DMP 266-005). Two Phase III pivotal studies were conducted by the applicant, DMP 266-006 and DMP 266-020, in HIV infected patients to compare efavirenz-containing combination regimens to triple therapy combination regimens. DMP 266-006 was designed as a randomized, open label trial comparing 3 combination regimens: 600 mg efavirenz QD +1000 mg indinavir Q8H, 600 mg efavirenz QD + 300 mg ZDV/150 mg 3TC Q12H and 800 mg indinavir Q8H + 300 mg ZDV/150 mg 3TC Q12H. DMP 266-020 was a randomized, double-blind, placebo-controlled study in HIV infected patients with prior exposure to NRTIs. Patients were randomized to one of 2 treatments: 600 mg efavirenz QD+1000 mg indinavir Q8H+NRTIs or 800 mg indinavir Q8H plus NRTIs. A third Phase III study, Study ACTG 364, was a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of 600 mg QD efavirenz + 750 mg Q8H nelfinavir + NRTIs in HIV infected patients.

SYNOPSIS

CHEMISTRY

Efavirenz belongs to the class of non-nucleoside reverse transcriptase inhibitors and is indicated in the treatment of HIV infection. The drug substance consists of a white to slightly pink, non-hygroscopic cystalline material and has a molecular weight of 315.68. Four crystalline forms have been identified (Form I, II, III and IV), of which I, II and III are polymorphs. For IV is a non-stoichiometric heptane solvate. Form I is the thermodynamically stable crystalline form. All clinical studies have used Form I. Efavirenz is practically insoluble in water (9 µg/ml at a pH of 8.3 and room temperature). The partition coefficient between octanol and water is log P=5.4.

MASS BALANCE

A mass balance study was conducted in 6 healthy, white males between the ages of 27 and 38. Each subject received daily oral doses of 400 mg (4x100 mg) efavirenz for 7 days. On the morning of Day 8, each subject received a single oral dose of 400 mg efavirenz labeled with 200 µCi of [14C]efavirenz as 4 capsules, each containing 100 mg efavirenz and 50 µCi of [14C]efavirenz. Efavirenz dosing (400 mg QD) continued for 20 days after administration of the radiolabeled material, with the last dose being administered on Day 28. Blood samples, urine and feces were collected for analysis over the 21 day period after administration of the radiolabeled material.

Plasma pharmacokinetic parameters (Mean and SD (n=6)) for total radioactivity, [14C]efavirenz, and efavirenz metabolites are shown below.

PK parameters	Total radioactivity	[14C]efavirenz	M1 [c]	M3/M7 [c]	M14[c]
C_{max} (µM)	2.60 (0.62)	1.35 (0.19)	0.84 (0.64)	0.41 (0.42)	0.09 (0.07)
T_{max} (hours)[a]	6.5 (3 – 12)	4.5 (3 - 8)	8.0 (3 - 12)	48 (16 – 72)	4.0 (4 – 12)
AUCÂ (µM*h)	337.61(61.63)	65.57 (15.88)	70.7 (26.2)	40.6 (29.1)	6.1 (4.2)
% total radioactivity	-	19.5 (4.2)	19.8 (5.1)	11.0 (6.9)	1.7 (1.0)
$T_{1/2}$[b] (hrs)	163.8 (40.6)	44.4 (22.7)	70.4 (48.4)	58.6 (16.3)	46.1 (19.6)

[a] Median (range) [b] Harmonic Mean and standard deviation [c] n=3 (subjects 1, 5, 6)

The mean urinary recovery of total radioactivity was 25% ± 8.3%, the fecal recovery was 41% ± 20.1%, and the total recovery was 66% ± 27% of the administered dose over 21 days.

No quantifiable concentrations of labeled efavirenz were detected in the urine and the majority of the radioactivity present in urine was attributed to the 8-hydroxy efavirenz glucuronide (M1) metabolite (86% of the total radioactivity in urine). Other minor urinary metabolites were identified as the 8-hydroxy efavirenz glucuronide (M14) and 7-OH efavirenz sulfate (M7) metabolites. Intact [14C]efavirenz accounted for the majority of total radioactivity measured in feces over 120 hours (over 90% of total fecal radioactivity). Small amounts (2% of the dose) of the 8-OH efavirenz (M4) metabolite were also detected in feces. The applicant did not attempt to determine the presence of efavirenz N-glucuronide (M2), 7-OH efavirenz (M5), or 7-OH efavirenz glucuronide (M6). Low concentrations of these metabolites have been observed in other studies.

SINGLE DOSE, HEALTHY VOLUNTEERS

In Study DMP 266-001, single doses of efavirenz ranging from 100 mg to (b)(4)----------- (b)(4)----------------althy adult male volunteers. Two different formulations -------------------------- -----------------------capsules) were used. The increases in AUC and Cmax were less than dose proportional across the efavirenz dose le(b)(4)---------------------------------ministration of the solid-filed capsules, meangSD AUC_{48} ranged--- µM*hr and mean Cmax ranged(b)(4)--------------------------------- ---- Apparent oral clearance of efavirenz increased with dose, most likely due to diminished absorption at higher doses (efavirenz aqueous solubility is very low, 9.2 µg/mL at 25ºC and pH 8.7, increasing at pH>9). The terminal half-life was very long; the 48 hour blood collection period was not adequate for assessing elimination. In t(b)(4)-------ct portion of this study, the blood sampling period was extended and T½ for the--------------capsule in the fasted state was approximately 76 hours. Based on the results of this study, the (b)(4)------ capsules were selected for subsequent clinical studies.

MULTIPLE DOSE, HEALTHY VOLUNTEERS

In Study DMP266-002, the safety, tolerability, and pharmacokinetics of multiple doses of efavirenz were assessed in healthy adult males. Cohort I subjects (n=5) received 200 mg efavirenz once daily (fasting) on Study Days 2-11. No medication was given on Days 1 and 12. Subjects in Cohort II (n=5) received 100 mg efavirenz BID (with "normal meals") on Days 2-11 and also received a single 800 mg dose of indinavir on Days 1 and 12. Trough efavirenz concentrations suggest steady state was achieved during this study. The steady-state AUC24 and Cmax values were 74.41 ± 17.03 µM*hr and 4.84 ± 1.07 µM, respectively, for the 200 mg QD regimen and were 80.45 ± 19.86 µM*hr and 4.55 ± 0.98 µM for the 100 mg bid regimen. The T½ was approximately 57 hours, suggesting there may be autoinduction of efavirenz with multiple dosing. Urine samples from another cohort on Day 11 were assayed for efavirenz, 8-hyroxy efavirenz, and the glucuronide conjugate of 8-hydroxy efavirenz. Less than 1% of the dose was excreted into the urine as efavirenz or 8-hydroxy efavirenz (M4). The glucuronide metabolite (M1) accounted for 66% of the administered dose.

A study (DMP266-025) was conducted in 24 healthy, adult males between the ages of 20 years and 42 years to compare the pharmacokinetics of efavirenz administered daily in the morning versus at bedtime. This study utilized a single-center, randomized, open-label, two period, crossover design. Subjects in Cohort I (n=12) received either 10 daily morning doses of 400 mg efavirenz in Period 1 followed by 10 daily bedtime doses of 400 mg efavirenz in Period 2 (Sequence A) or vice-versa (Sequence B). Subjects in Cohort II (n=11) received either 10 daily morning doses of 600 mg efavirenz in Period 1 followed by 10 daily bedtime doses of 600 mg efavirenz in Period 2 (Sequence A) or vice-versa (Sequence B). The two 10-day periods for Groups 1 and 2 for both cohorts were separated by an interval of 32 hours.

Mean g SD Pharmacokinetic Parameters for Each Treatment

Dose	Cmin (µM)	Cmax (µM)	Tmax (hr)	AUCT (µM)	CL/F (L/hr)
400 mg QD (AM)	6.284 g3.769	13.016 g 5.095	4.083 g 0.515	203.593 g 97.073	7.494 g3.001
600 mg QD (AM)	4.933 g 1.785	13.243 g 2.835	3.818 g 0.982	188.101 g 55.965	10.831 g 2.821
400 mg QD (PM)	6.200 g 2.970	13.157 g 6.925	4.086 g 1.993	188.729 g 89.139	8.629 g 6.912
600 mg QD (PM)	5.672 g 1.754	13.119 g 3.117	3.833 g1.528	196.251 g 49.973	10.272 g 2.651

At the 400 mg dose of efavirenz, there were no significant differences in the pharmacokinetic parameters between morning and bedtime dosing. For the 600 mg dose, statistically significant differences were found between morning and bedtime dosing for C_{min} and AUC(0-T). However, these differences are relatively small.

Comparison of the pharmacokinetic parameters between the 400 mg and 600 mg dose groups indicated a lack of dose proportionality; mean C_{max}, AUC(0-T) and C_{min} values were similar at both doses. However, a comparison across studies indicates that efavirenz pharmacokinetic parameters are dose proportional. The pharmacokinetic parameters were compared between the two study periods. When data for both dose groups were combined, a statistically significant period effect was observed for AUC(0-T) and C_{min}, with values being slightly lower for Period 2 compared to Period 1. These results suggest that the induction of efavirenz metabolism may not be complete after 10 days of dosing.

The results from this study suggest that AUC(0-T) and C_{min} following bedtime 600 mg efavirenz dosing are slightly higher than morning dosing. These differences are small and may not have any clinical significance. The period effects observed in this study suggest that efavirenz induces its own metabolism following multiple doses. Efavirenz T1/2 is decreased following multiple doses (57 hours) compared to the T1/2 following single doses 76 hours), which also suggest autoinduction.

MULIPLE DOSE, HIV-INFECTED PATIENTS

Potential differences in the pharmacokinetics of efavirenz between patients and healthy volunteers were evaluated by pooling data from multiple dose studies in these populations. Statistically significant differences were found for Cmax, AUC(0-T) and Cl/F between HIV-infected patients and healthy volunteers at the 600 mg daily dose of efavirenz. These differences are small and are probably not clinically significant. The analyses suggested that healthy volunteers had a lower Cl/F compared to patients. Most of this difference was due to the differences between Black patients and Black volunteers; there were no differences in efavirenz pharmacokinetics between Caucasian patients and volunteers. The differences between Black patients and healthy volunteers may be due to decreased absorption of efavirenz in patients or decreased compliance by patients in taking medication. Also, the autoinduction effect may be more fully expressed in patients since pharmacokinetic assessments were performed at day 14 or later, whereas most volunteer studies had pharmacokinetic measurements at day 7-10.

Mean g SD Efavirenz PK Parameters in Patients and Healthy Volunteers (Pooled Analyses)

PK Parameter	Dose (mg)	HIV infected Patients	Healthy Volunteers
Cmax (µM)	200	4.99 g1.54; N=48	4.66 g 0.93; N=26
	400	9.64 g4.31; N=33	10.70 g 3.67; N=87
	600	12.94 g3.67; N=35	15.64 g 4.99; N=42
AUC(0-T) (µM.h)	200	67.8 g 23.5; N=48	75.1 g 17.4; N=26
	400	146.0 g 77.7; N=33	162.9 g 67.7; N=87
	600	184.2 g 72.9; N=35	237.9 g 94.0; N=42
Cl/F (L/hr)	200	10.4 g 3.39	8.89 g 2.09
	400	10.64 g 4.59	8.94 g 3.11
	600	11.86 g 4.38	9.04 g 3.06

BIOAVAILABILITY/BIOEQUIVALENCE

The applicant has conducted three bioavailability/bioequivalence studies which are described below.

A pi(b)(4)--------bility study DMP266-012 was conducted to evaluate two formulations relative to the ----------------capsule (clinica(b)(4)------------------------as the reference formulation. One test formulation w--(100 mg capsule) and the other was manufactured--------------------------(100 mg and 200 mg). Subjects received a 200 mg single dose of the test or reference capsule in a randomized two-way crossover fashion after an overnight fast. Blood samples were collected from 0 to 168 hours to determine efavirenz pharmacokinetics. Three cohorts were (n=13 per cohort) enr((b)(4)-----------------lation was tested in each cohort. (b)(4)--------------nstrated that the 100 mg------------------------- capsule formula(b)(4)-------- 200 mg ----------------------capsule ((b)(4)--------------- bioequivalent to the 100 mg -----------------capsule (b)(4)-------- The 100 mg ----------------------capsule formulation was bioequivalent to the 100 mg ---------------capsule formul----------------------- to AUC, but not with respect to C_{max} (90% CI: 9(b)((b)(4)--------was decided that to-be-marketed capsules would be manufactured by the 4)-- ---------------process.

A bioequivalence study (DMP266-041) was conducted to compare efavirenz capsules manufactured from two lots that showed differing dissolution profiles at the early time points. The objective was to compare the rate and extent of absorption of efavirenz from the two lots and to assess if there was any correlation between the observed dissolution profiles and bioavailability.

The dissolution profiles for capsules manufactured from A were consistently slower at the 10 and 15 minute time points than the profile for capsules manufactured from B. However, at 30 minutes, the dissolution profile for capsules manufactured from A showed nearly 100% of drug dissolved, which was similar to the dissolution profile for capsules manufactured from other lots.

Lot Number	Percent Dissolved : Mean (SD)				
	10 min	15 min	30 min	45 min	60 min
Drug Substance Lot SB706-023 (A)	47.5 (6.3)	73.6 (6.5)	99.4 (1.3)	100.4 (0.6)	100.6 (0.6)
Drug Substance Lot SB706-021 (B)	93.8 (4.6)	99.4 (1.6)	100.4 (0.9)	101.1 (1.0)	101.4 (0.9)

The bioequivalence study was a 2-way crossover study in which subjects were randomized to one of 2 sequences. There was a 28-day washout between the two study periods. Doses were administered in the morning under fasted conditions.

Mean (SD) Efavirenz PK : Test Lot SB706-023 (1x200 mg) vs. Reference Lot SB706-021 (1x200 mg)

PK parameter	Test Lot SB706-023 (n=28)	Reference Lot SB706-021 (n=28)	Ratio (Test/Ref)	90% CI
Cmax (µM)	3.66 (0.94)	3.53 (0.78)	1.030	(95.1, 111.7)
AUC (µM.h)	148.3 (46.7)	147.5 (41.9)	0.995	(96.0, 103.2)

Bioequivalence was demonstrated for Cmax and AUC between the 200 mg capsule from Drug substance Lot SB706-023 (test) to capsules manufactured from drug substance Lot SB706-021 (reference). These data suggest the lack of *in-vitro in-vivo* correlation between the dissolution test results at the 10 min and 15 min time points for the 2 lots and bioequivalence. These results are not unexpected since efavirenz peak concentrations are observed only 4 –5 hours post-dose and it has a very long terminal half-life.

The **pivotal bioequivalence study** (DMP266-026) was conducted in healthy, adult males (21) and females (9) between the ages of 18 years and 46 years. Of these, 28 were included in the pharmacokinetic analysis. This study utilized a single-center, randomized, open-label, three period, crossover design . Each subject received a single 200 mg dose of each of the three following treatments:
Treatment A: Efavirenz 200 mg (2x100 mg : micronized clinical formulation): Reference
Treatment B: Efavirenz 200 mg (2x100 mg : commercial wet granulation formulation): Test
Treatment C: Efavirenz 200 mg (1x200 mg : commercial wet granulation formulation): Test

There was a 28-day washout period between each dose administration. Bioequivalence of the test and reference formulations was assessed using 90% confidence intervals (CI) on the differences in mean LnAUC and Ln C_{max}.

Mean (SD) Efavirenz PK

PK parameter	Test Commercial 2x100 mg (n=28)	Test Commercial 1x200 mg (n=28)	Reference (Clinical 2x100 mg) (n=28)
Cmax (µM)	3.40 (0.80)	3.41 (1.01)	2.81 (0.76)
AUC (µM.h)	165.0 (48.2)	158.5 (51.3)	140.3 (39.2)

Mean Ratios for Log-Transformed AUC and Cmax (Test-to-Reference)

	Ln AUC (B/A)	Ln AUC (C/A)	Ln C_{max} (B/A)	Ln C_{max} (C/A)
Geometric Mean	1.16	1.14	1.21	1.22
90% CI	(109, 122)	(108, 120)	(112, 136)	(110, 134)

The pharmacokinetic parameters were similar for both the 100 mg and the 200 mg commercial (test) capsule formulations. T_{max} for all the formulations occurred approximately 3 hours post-dose. The 90% CI for differences in the log transformed AUC_{0-} between test and reference were within the (b)(4)------goal posts for both test formulations. However, the upper limits of the 90% CI for log transformed C_{max} were higher than the acceptable criterion (b)(4)---- Therefore bioequivalence was demonstrated with respect to AUC, but not with respect to C_{max}. The C_{max} values for both test (commercial) formulations were approximately 21% higher than that of the reference (clinical) formulation. The commercial capsules were used in some clinical trials. The applicant attempted to evaluate whether the higher C_{max} resulting from the commercial formulation had an effect on the rate of adverse events, by comparing the frequency of reported adverse events in patients in clinical trial DMP266-006. The rate of adverse events was compared between those who started efavirenz therapy with the clinical formulation (n=261) and those who started therapy with the commercial formulation (n=107). No significant differences were observed in the incidence of AE's between the two formulations.

The 100 mg and 200 mg commercial capsule formulations of efavirenz are bioequivalent to the efavirenz 100 mg capsules used in clinical trials with respect to AUC, but not with respect to C_{max}. This difference does not appear to be clinically significant. The proposed commercial formulation was used in clinical trials.

FOOD EFFECT

The effect of food on the pharmacokinetics of efavirenz (b)(4)-- capsules) administered as a 1200 mg single dose was investigated in Study DMP 266-001. Five subjects per form(b)(4)---------administered 1200 mg efavirenz, both fasted and with a high fat (b)(4)-When the------------------ formula(b)(4)---------------------d, there was a 69 ± 43%(b)(4)----------------- increase in AUC ∞, an 86 ± 75% --------------------------increase in Cmax, and Tmax was approximately 2 hour(b)(4)---------------------- When the (b)(4)-------formulati(b)(4)--------------------- there was a 62 ± 40% -----------------------------increase in AUC , an 81 ± 30%---------------------------- increase in Cmax, and Tmax was approximately 1 hour later in the fed state.

In Study DMP266-002, Cohort I subjects (n=5) received 200 mg efavirenz once daily (fasting) on Study Days 2-11. No medication was given on Days 1 and 12. Subjects in Cohort II (n=5) received 100 mg efavirenz BID (with "normal meals") on Days 2-11. The AUC_{24} at steady-state was similar for the two Cohorts.

In Study DMP 266-019 (nelfinavir interaction study), efavirenz 600 mg QHS was administered following a light snack. In Study DMP 266-029 (rifampin interaction study), efavirenz 600 mg QHS was administered 2 hours after a meal. The pharmacokinetic parameters for efavirenz were similar for both studies.

The applicant concluded that efavirenz can be administered without regard for food. However, due to the potential for large increases in efavirenz concentrations, efavirenz should not be coadministered with a high fat meal.

SPECIAL POPULATIONS

GENDER

Potential differences in the pharmacokinetics of efavirenz between males and females were evaluated by pooling data from single and multiple dose Phase 1 studies. For single dose studies, the sample size was adequate only for the comparison at the 200 mg dose level (93 males and 24 females). No significant differences were found for Cmax, AUC and Cl/F between males and females. For multiple dose studies, the sample size was adequate only for the comparison at the 400 mg dose level (71 males and 16 females). No significant differences were found for Cmax, AUC and Cl/F between males and females. Efavirenz pharmacokinetics were not compared between male (n=100) and female (n=16) HIV infected patients since there were an insufficient number of HIV positive females to perform a statistical analysis. An analysis of the cumulative frequency distribution of Cl/F with respect to gender for all subjects and patients who received multiple doses of efavirenz showed no differences between males and females. The oral clearance of efavirenz in HIV infected males was similar to that in HIV infected females. This observation is reflected in the efavirenz label which states that there was no effect of gender on efavirenz pharmacokinetics in HIV infected patients.

RACE

The effect of race on the pharmacokinetics of efavirenz was evaluated by pooling data from single and multiple dose Phase 1 studies. The only racial groups with a sufficient number of subjects for analysis were the Caucasian and Black groups. In healthy volunteers, the AUC was significantly increased and the CL/F was decreased following a single 400 mg dose of efavirenz in Blacks (n=9) compared to Caucasians (n=17). Similar results were seen following multiple doses of 400 mg (31 Blacks and 50 Caucasians) and 600 mg (14 Blacks and 20 Caucasians) efavirenz to healthy volunteers.

An analysis of the cumulative frequency distribution of Cl/F with respect to race for all subjects and patients across doses following multiple doses of efavirenz showed significant differences between Blacks and Caucasians. When the analysis was done separately for HIV infected patients, there appeared to be no differences between Black (n=31) and Caucasian (n=75) patients. The analysis indicated that Caucasian healthy volunteers, Caucasian patients and Black patients had similar Cl/F. However, the Black healthy volunteers had a decreased Cl/F and were different from the other groups. The oral clearance of efavirenz in HIV infected Blacks was similar to that in HIV infected Caucasians. This observation is reflected in the efavirenz label which states that there was no effect of race on efavirenz pharmacokinetics in HIV infected patients.

Population pharmacokinetic analysis of healthy volunteers showed that Blacks and Asians had reduced clearance compared to Caucasians. When the analysis was performed in patients, Blacks were not found to be different from Caucasians, however, the Asian race remained a significant covariate (there were only 2 Asian patients in the analysis). Further information in Asian HIV infected patients would be necessary to confirm this finding.

PEDIATRICS

ACTG 382 was a 48-week, Phase I/II, single-arm, AUC-controlled, multi center study in which 57 HIV-infected children (3 to 16 years of age, and able to swallow capsules) were treated with efavirenz + nelfinavir (30 mg/kg tid), in addition to nucleoside reverse transcriptase inhibitors. The objectives of this study were to: 1) determine the dosing regimen of efavirenz in combination with nelfinavir in children; 2) study the safety profile of this combination in children; 3) characterize the antiretroviral activity and the effect on CD_4 counts of this combination in children. The initial dose was 600 mg of efavirenz, adjusted for body size using the formula: Initial efavirenz dose = (Weight in kg/70 kg)$^{0.7}$ x 600 mg daily. The targeted AUC was between 190 µM.h and 380 µM.h. This dose was adjusted according to a specific algorithm on the basis of tolerability and efavirenz plasma concentrations after 2 weeks of therapy. If the dose was well tolerated, but the efavirenz AUC values were too low, the dose was increased. If the dose was not well tolerated and the efavirenz AUC values were too high, the dose was decreased by prorating it to achieve an AUC of 285 µM.h. Twenty-four hour pharmacokinetic profiles were obtained at Week 2 and Week 6.

Comparison of Week 2 Pharmacokinetic Data in Children to Historical Pharmacokinetic Data in Adults

PK Parameter	HIV-infected adults (n=35): Mean (SD)*	HIV-infected children (n=48): Mean (SD)
C_{max} (µM)	12.9 (3.7)	14.2 (5.8)
C_{min} (µM)	5.6 (3.2)	5.6 (4.1)
AUC(0-T) ((µM.hr)	184 (73)	218 (104)

* Data from studies 266-003, 266-004, 266-021.

The pharmacokinetic data from Week 2 in pediatric patients showed that dose adjustments were indicated in 29 patients (25 increases and 4 decreases), while 20 patients needed no dose adjustment. The exposure to efavirenz for HIV-infected children receiving a 600 mg body size-adjusted dose at Week 2 (before any dose adjustments) were compared to the exposure to efavirenz in HIV-infected adults receiving 600 mg QD. The comparison suggests that the mean C_{max} and AUC(0-T) for the two groups are similar, although somewhat higher in children compared to adults.

After dose adjustments were made for 17 patients at Week 4, pharmacokinetics were obtained again at week 6 for all patients. At week 6, the mean C_{max}, C_{min}, and AUC(0-T) in 41 children were 16.7 µM, 5.9 µM and 246 µM.hr, respectively. The Week 6 pharmacokinetic parameters were higher than those from Week 2, consistent with the fact that doses were increased in most of the patients who needed dose adjustments. (Note: In adults, nelfinavir caused a non-significant (~12%) decrease in efavirenz AUC.)

The following dosing nomogram was constructed to provide similar efavirenz doses as those administered in study ACTG 382. Since only the 50 mg and 100 mg capsules are being commercialized, the recommendations are being made in 50 mg increments.

Body weight (kg)	Efavirenz dose (mg)
13-15	200
15-20	250
20-25	300
25-32.5	350
32.5-40	400
> 40	600

The recommended dosing schedule will provide slightly higher plasma levels of efavirenz than the dosing schedule in this study, because results from this study suggested that some patients had a lower exposure to efavirenz. Also, it was necessary to change the dosing regimen from the one used in this study, due to the capsule strengths that will be commercially available.

The dosing nomogram is appropriate because: 1) efavirenz pharmacokinetics in children receiving 600 mg adjusted for body size was similar to that in adults receiving a 600 mg dose; 2) the initial doses demonstrated antiviral activity and there was no obvious dose-related toxicity. A dose of 600 mg has been suggested for children heavier than 40 kg since adults greater than 40 kg have been given 600 mg efavirenz in clinical studies.

ELDERLY

The pharmacokinetics of efavirenz have not been studied in adults over the age of 65.

RENAL IMPAIRMENT

The pharmacokinetics of efavirenz have not been studied in patients with renal impairment. However, less than 1% of efavirenz is excreted unchanged in the urine; therefore, dosage adjustment for efavirenz in renal insufficiency should not be necessary.

HEPATIC IMPAIRMENT

The effect of chronic liver disease on efavirenz pharmacokinetics is being evaluated in Study DMP 266-033. Three chronic liver disease patients and three matched control subjects had completed the study at the time of submission of the interim report. The 3 patients were enrolled with a diagnosis of cirrhosis proven by biopsy or ultrasound. Indocyanine green (ICG) clearance, an indicator of functional hepatic blood flow, was determined the day prior to administration of a single 400 mg dose of efavirenz. The ICG clearance and terminal rate constant were significantly decreased in the patients compared to the matched controls. Efavirenz pharmacokinetics following a single 400 mg dose were compared between patients and controls. There was an increase in the AUC and a decrease in the terminal rate constant of efavirenz for the liver disease patients compared to healthy controls. The patients also had lower Cmax and a later Tmax compared to controls. These preliminary results suggest that there may be changes in efavirenz absorption and/or disposition in hepatically impaired patients. Additional data are needed to draw any conclusions concerning the effect of hepatic impairment on efavirenz pharmacokinetics.

Efavirenz Pharmacokinetic Parameters as Mean (SD) Following a 400 mg Dose to Patients with Chronic Liver Disease and Healthy Matched Controls

PK Parameter	Liver disease Patients (n=3)	Healthy Matched Controls (n=3)
Cmax (µM)	3.71 (0.95)	5.92 (0.51)
Tmax (hr)	5.0 (3.0-5.0)	3.0 (2.0-3.0)
AUC (µM.h)	333.7 (120.4)	256.8 (9.9)
ìn (h^{-1})	0.0045 (0.001)	0.0073 (0.001)
T1/2 (hr)	154 (31)	94.9 (13.0)
Cl/F (L/h)	4.1 (1.24)	4.94 (0.19)
fu	0.0021 (0.0007)	0.0024 (0.0009)

DRUG INTERACTIONS

Drug interaction studies were conducted with efavirenz and drugs that have the potential to interact with it. Studies were also conducted with some drugs expected to be coadministered with efavirenz. Efavirenz is an inducer of CYP3A4 and may induce CYP2B6. Efavirenz may also inhibit CYP3A4, CYP2C9, and CYP2C19. Efavirenz is metabolized by CYP3A4 and CYP2 B6, with subsequent glucuronidation. In addition to metabolic interactions, the potential for pharmacokinetic changes due to altered gastric pH was evaluated.

Results From Drug Interaction Studies- The Effect of Efavirenz on Other Drugs

Coadministered Drug	Dose	Efavirenz Dose	Coadministered Drug (% Change)		N	Study
			AUC mean (90%CI)	Cmax mean (90%CI)		
Indinavir	800 mg Q8H x 14d	200 mg QD x 14d	⇓31% (13, 45)	⇓16% (-10, 30)	27	003
Nelfinavir Metabolite (AG-1402)	750 mg Q8H x 7d	600 mg QD x 7d	⇑20% (8, 34) ⇓37% (25, 48)	⇑21% (10, 33) ⇓40% (30, 48)	7	019
Ritonavir	500 mg q12h x 8d a.m. dose p.m. dose	600 mg QD x 10d	 ⇑18% (6, 33) ⇔	 ⇑24% (12, 38) ⇔	11	011
Saquinavir SGC	1200 mg Q8H x 14d	600 mg QD x 10d	⇓62% (45, 74)	⇓50% (28, 66)	25	036
Lamivudine	150 mg q12h x 14d	600 mg QD x 14d	⇔	⇔	10	004
Zidovudine	300 mg q12h x 14d	600 mg QD x 14d	⇔	⇔	10	004
Azithromycin	600 mg single dose	400 mg QD x 7d	⇔	⇑22% (4, 42)	14	018
Clarithromycin 14-OH clarithromycin	500 mg q12h x 7d	400 mg QD x 7d	⇓39% (30, 46) ⇑34% (18, 53)	⇓26% (15, 35) ⇑49% (32, 69)	11	016
Fluconazole	200 mg QD x 7d	400 mg QD x 7d	⇔	⇔	10	015
Ethinyl estradiol	50 µg single dose	400 mg QD x 10d	⇑37% (25, 51)	⇔	13	017

Results From Drug Interaction Studies- The Effect of Other Drugs on Efavirenz

Coadministered Drug	Dose	Efavirenz Dose	Efavirenz % change		N	Study
			AUC mean (90%CI)	Cmax mean (90%CI)		
Indinavir	800 mg Q8H x 14d	200 mg QD x 14d	⇔	⇔	27	003
Nelfinavir	750 mg Q8H x 7d	600 mg QD x 7d	⇔	⇔	10	019
Ritonavir	500 mg q12h x 8d	600 mg QD x 10d	⇑21% (10, 24)	⇑14% (4, 26)	11	011
Saquinavir SGC	1200 mg Q8H x 14d	600 mg QD x 10d	⇓12% (4, 19)	⇓13% (5, 20)	25	036
Rifampin	600 mg QD x 7d	600 mg QD x 7d	⇓26% (15, 36)	⇓20% (11, 28)	12	029
Azithromycin	600 mg single dose	400 mg QD x 7d	⇔	⇔	14	018
Clarithromycin	500 mg q12h x 7d	400 mg QD x 7d	⇔	⇑11% (3, 19)	12	016
Fluconazole	200 mg QD x 7d	400 mg QD x 7d	⇑16% (6, 26)	⇔	10	015
Famotidine	40 mg single dose	400 mg single dose	⇔	⇔	18	014
Mylanta DS	30 mL single dose	400 mg single dose	⇔	⇔	18	014
Ethinyl estradiol	50 µg single dose	400 mg QD x 10d	⇔	⇔	13	017

ANTIRETROVIRAL DRUGS

Indinavir : Coadministration of 200 mg QD efavirenz with 800 mg or 1000 mg Q8H indinavir resulted in a 30 to 35% decrease in indinavir exposure. The 1000 mg indinavir dose when given with 200 mg QD efavirenz resulted in indinavir exposure that was similar to that following indinavir alone at 800 mg Q8H. Indinavir, at doses of 800 and 1000 mg Q8H, does not alter the pharmacokinetics of efavirenz.

The pharmacokinetics of indinavir were assessed when indinavir at a dose of 1200 mg Q8H was coadministered with different doses of efavirenz (200 mg, 400 mg, and 600 mg). Indinavir mean C_{max} and AUC(0-T) appeared to be similar in each case, indicating that there are no dose-related effects of efavirenz on indinavir pharmacokinetics. The induction of indinavir metabolism by efavirenz is similar at daily doses of 200, 400 and 600 mg.

In one study (DMP 266-021), coadministration of efavirenz 600 mg QHS with indinavir 1000 mg Q8H resulted in lower than expected indinavir concentrations. The indinavir pharmacokinetics were determined for the evening dose of indinavir; indinavir diurnal variation has not been studied previously. The results from this study do not agree with results from other drug interaction studies with indinavir and efavirenz. The reasons for this disagreement have not been explained. Note: The pivotal clinical trials for efavirenz included indinavir in combination with efavirenz.

Nelfinavir: Nelfinavir at a dose of 750 mg Q8H did not alter the steady state AUCτ or Cmax of efavirenz at a dose of 600 mg QHS. Efavirenz at dose of 600 mg QHS increased nelfinavir AUCτ by approximately 20% and Cmax by approximately 21%. The results were similar when efavirenz 400 mg QD was administered with nelfinavir 750 mg Q8H. The changes observed in this study were not clinically significant. Efavirenz and nelfinavir may be coadministered without adjusting the dose of either drug.

Ritonavir: Ritonavir at a dose of 500 mg Q12H statistically significantly increased steady state efavirenz AUCτ, Cmax and Cmin by approximately 15-25%. Efavirenz at dose of 600 mg QHS statistically significantly increased ritonavir AUC, Cmax and Cmin. These parameters increased by approximately 17-24%, although the morning trough concentration increased by 42%. Adverse events, such as rash and altered sensorium, increased in rate when efavirenz and ritonavir were coadministered relative to when either drug was administered alone. Several subjects experienced increased liver enzymes when efavirenz and ritonavir were coadministered. Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.

Saquinavir: Concomitant administration of efavirenz (600 mg QD) and saquinavir soft gel capsules (1200 mg Q8H) enhances the metabolism of saquinavir resulting in a reduction of saquinavir 24 hr-AUC and Cmax by approximately 62% and 50%, respectively. Because of the reduction in saquinavir levels, saquinavir should not be used as the sole protease inhibitor in combination with efavirenz.

Lamivudine: There was no consistent indication of a drug interaction when efavirenz (400 mg QD or 600 mg QD) and lamivudine (150 mg Q12H) were coadministered. There was a significant 17% decrease in lamivudine AUC(0-T) in the 400 mg efavirenz group. The 600 mg dose group showed the opposite trend, where, the lamivudine AUC(0-T) increased 15% relative to baseline. The data from the drug interaction study suggest that efavirenz, when coadministered with lamivudine, does not clinically significantly affect the pharmacokinetics of lamivudine. Efavirenz pharmacokinetics were not significantly altered when given concomitantly with lamivudine.

Zidovudine: The pharmacokinetics of zidovudine and efavirenz were not altered significantly when efavirenz (400 mg QD) and ZDV (300 mg Q12H) were coadministered.

INTERACTION STUDIES WITH CYP3A4 SUBSTRATES AND INDUCERS

Rifampin: Coadministration of rifampin 600 mg QD and efavirenz 600 mg QHS resulted in a statistically significant decrease in efavirenz AUC (26%) and Cmax (20%). However, for 2 of 12 subjects, efavirenz concentrations did not decrease with concomitant rifampin. Rifampin concentrations were similar to historical data. There are inadequate safety data to recommend a higher dose of efavirenz when coadministered with rifampin. Based on efficacy data, efavirenz and rifampin can be used in combination.

Clarithromycin: Coadministration of clarithromycin 500 mg Q12H with efavirenz 400 mg QD resulted in an 11% increase in efavirenz C_{max}, a 39% decrease in clarithromycin AUC and a 26% decrease in clarithromycin Cmax. Although concentrations of the active metabolite 14-OH clarithromycin increased when efavirenz and clarithromycin were coadministered, the combined AUC for clarithromycin + metabolite when efavirenz was present was less than the combined

AUC when efavirenz was not present. The small increase in efavirenz Cmax is not considered important. It is not known whether the 39% decrease in clarithromycin AUC when efavirenz is coadministered is clinically important. Also, the incidence of rash was increased when clarithromycin and efavirenz were coadministered. For patients receiving efavirenz, alternatives to clarithromycin, such as azithromycin, should be considered.

Ethinyl estradiol: Coadministration of efavirenz 400 mg QD with a single 50 µg dose of ethinyl estradiol resulted in a 37% increase in ethinyl estradiol AUC∞. There was no change in efavirenz pharmacokinetic parameters. Although efavirenz did not decrease ethinyl estradiol concentrations, it is difficult to extrapolate the results of this study to multiple doses of combination oral contraceptives. A reliable method of barrier contraception should be used in addition to oral contraceptives.

INTERACTION STUDIES WITH OTHER COMMONLY PRESCRIBED THERAPIES

Azithromycin: Coadministration of efavirenz 400 mg QD with a single 600 mg dose of azithromycin does not result in a clinically significant interaction, no dosing adjustment is needed.

Fluconazole: Fluconazole at a dose of 200 mg QD increased efavirenz AUC by approximately 16%, which is not considered clinically significant. Efavirenz at a dose of 400 mg QD did not alter the steady-state pharmacokinetic parameters of fluconazole. Fluconazole and efavirenz may be co-administered without adjusting the dose of either drug.

Antacids/famotidine: Efavirenz concentrations following administration of 400 mg efavirenz either 1 minute after 30 mL Mylanta or 1 hour after 40 mg famotidine were similar to concentrations observed following administration of efavirenz alone. These results suggest that alteration of gastric pH does not affect efavirenz absorption.

METABOLISM

METABOLITES IN PLASMA AND URINE

Efavirenz was extensively metabolized by humans; trace quantities of the parent compound were excreted in the urine. The major metabolite excreted in urine was the glucuronide conjugate of the 8-OH efavirenz (M1) metabolite. This indicated that 8-hydroxylation followed by glucuronidation was the major pathway of efavirenz metabolism. Very small quantities of 8-OH efavirenz (M4) were eliminated in the urine of humans dosed with efavirenz. Efavirenz was also metabolized by direct conjugation with glucuronic acid forming the N-glucuronide (M2), which was also found in human urine samples of subjects exposed to efavirenz. The glucuronide conjugate of 7-OH efavirenz (M6) and 7-OH efavirenz sulfate (M7) were also found in human urine samples. The M1 metabolite was the most abundant metabolite in human plasma. In addition, 8-OH efavirenz sulfate (M3) and M7 were found in human plasma. Another metabolite, 8-OH efavirenz glucuronide cyclopropanol (M14) was also found in human plasma samples of efavirenz-treated subjects. All the metabolites identified in humans were also present in monkeys.

IN-VITRO METABOLISM

Human liver microsomes metabolized efavirenz to 8-OH efavirenz (M4). This was also observed in studies using microsomes from rats, rhesus monkeys and cynomolgus monkeys. For efavirenz 8-hydroxylation studies, human liver microsomes were incubated with 14C-efavirenz (0.45 µCi) at concentrations of 10 to 100 µM for 40 minutes followed by(b)(4)---------analysis. The K_m values determined for human microsomes from individual donors were 20.4 and 36.6 µM, respectively. Incubations using microsomes from a lymphoblastoid cell line selectively expressing human CYP isozymes were done. These studies showed that efavirenz is oxidized to M4 approximately 20 times faster by microsomes enriched with CYP2B6 than by microsomes enriched with CYP3A4. The significance of this finding in humans is unclear since CYP2B6 is a very minor form (<0.3% of total P450) in normal human liver. There was no activity observed with microsomes enriched with CYPs 2E1, 2C8, 2C9, 2C19, and 2D6.

CYP INHIBITION

Efavirenz was evaluated in-vitro for its inhibitory potency against a broad spectrum of human CYP enzymes. Studies were conducted to evaluate *in-vitro* inhibition of human liver CYP enzymes by efavirenz and its 8-hydroxy metabolite. Relative potency (Ki) and type of inhibition were determined for CYP enzymes 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 using the following enzyme-selective CYP reactions, respectively: phenacetin O-deethylation, tolbutamide hydroxylation, S-mephytoin 4'-hydroxylation, dextromethorphan O-demethylation, chlorzoxazone 6-hydroxylation and testosterone 6 â-hydroxylation. CYPs 2C9, 2C19, and 3A4 in human liver microsomes (n=2) were inhibited by efavirenz with Ki values of 8.5, 10, and 17 µM, respectively. Also, the M4 metabolite, 8-OH efavirenz, inhibited CYPs 2C9, 2C19, 2D6, and 3A4 with K_i values of 1, 10, 13, and 6 µM, respectively. Human liver microsomal glucuronidation was inhibited by efavirenz and M4 with Ki values of 0.39 and 0.25 mM, respectively. Since plasma concentrations of efavirenz in the clinical setting are expected to reach a maximum of 10 to 20 µM, interactions with drugs metabolized by CYPs 2C9, 2C19, and 3A4 may be clinically significant. However, it should be noted that efavirenz is approximately 99.5% bound to plasma proteins and that these experiments were not performed at concentrations equivalent to unbound plasma concentrations.

ANTIRETROVIRAL ACTIVITY OF METABOLITES

The M1 (8-OH efavirenz glucuronide) and M4 (8-OH efavirenz) metabolites were evaluated for activity against HIV-1 reverse transcriptase (RT). The M1 metabolite was inactive against HIV-1 RT. The M4 metabolite was approximately 37 times less active than efavirenz against HIV 1 RT.

IN-VITRO DISTRIBUTION STUDIES

PROTEIN BINDING

Efavirenz was found to be extensively bound to plasma proteins, predominantly albumin. The unbound fraction, as determined by ultrafiltration using 14C-efavirenz, averaged 0.5(b)(4)------an plasma. The percent unbound was independent of concentration over the range of-------------- µM. The unbound fraction, as determined by equilibrium dialysis with LC/MS/MS detection, averaged 0.31% in human plasma and was independent of concentration over the range(b)(4)--- (b)(4) The extent of binding to proteins in human plasma was also determin(b)(4)-------------- (b)(4)---------------------------- 2 healthy volunteer drug interaction studies using ------------------------- ---------------------------------- T(b)(4)---------------und was 0.22% and was independent of concentration over the range---------------------. In simulated human CSF to which efavirenz was added, the percent unbound was 58.8%. Addition of 100 mg/dL of human serum albumin to the simulated CSF decreased the unbound fraction to 14.6 %, suggesting that efavirenz binds to albumin.

CSF CONCENTRATION

CSF and plasma samples were collected from nine patients receiving efavirenz ((b)(4)--------- 004, 005, 006). CSF samples were analyzed by LC/MS/MS and plasma samples------------- (b)(4)-----------------------------CSF of these patients. The CSF/plasma mean ratio was 0.0069 ----------------------------------- The CSF/plasma ratio was approximately 3 times higher than the unbound fraction (0.0022) in plasma observed in healthy volunteers. The CSF/plasma ratio did not appear to be dependant on plasma concentrations.

RATIONALE FOR DOSE SELECTION

The applicant has chosen a dose of 600 mg QD for efavirenz based on the rationale that it is generally well tolerated and that this dose should provide adequate trough free drug concentrations to suppress all known viral variants with single reverse transcriptase ((b)(4)---- pair substitutions. IC90 for viral variants with single RT base pair substitutions range --------------

(b)(4)---and the 600 mg QD dose should provide trough concentrations in this range in the majority of the patients (>90%). The other clinically tested doses of efavirenz (200 mg and 400 mg QD) provide trough concentrations in the range of the IC90 in a lower percentage of patients. A dose ranging study, DMP 266-005, in which 200 mg, 400 mg and 600 mg (or placebo) of efavirenz were used in combination with ZDV and 3TC was conducted. This study failed to find differences in response rates between the 3 doses of efavirenz.

In the pivotal studies (other than the dose ranging study), the 600 mg QD dose of efavirenz was the only dose used. The 600 QD dose was found to be generally well tolerated and was the highest dose tested for safety and tolerability in patients. The 600 mg dose was the only dose that was used in pivotal trials and was shown (in combination with 2 NRTIs, a PI or both) to provide at least equivalent efficacy to the current standard of care.

ADVERSE EXPERIENCES

Adverse events (AE), of all severities (both related and not related to efavirenz) that were reported in more than 10% of patients who received 600 mg QD efavirenz (N=413) were nausea (29.1%), dizziness (26.6%), headache (23.5%), diarrhea (23.5%), fatigue (23%), vomiting (13.3%), rash (14.8%), insomnia (13.3%), dyspepsia (13.3%), influenza-like symptoms (12.1%), impaired concentration (11.4%) and pain (10.7%).

The AE rates in efavirenz-treated groups that were found be statistically significantly higher compared to the control-treated groups (n=297) included dizziness (26.6% vs 8.8%), rash (14.8% vs. 7.4%), impaired concentration (11.4% vs 4.4%), depression (9.4% vs 5.4%), nervousness (7.0% vs 3.4%), dreaming abnormal (5.6% vs 1.0%), euphoria (5.3% vs 1.7%) and asthma (1.7% vs. 0.0%).

In the clinical development program of efavirenz, two types of AEs were noted to occur with higher frequencies on efavirenz: central nervous system symptoms and rash. Approximately 54% of the 413 efavirenz-treated (600 mg QD) patients experienced one or more altered sensorium AE compared with 27% of the 297 control-treated patients. These AEs were usually mild to moderate in severity; the median time-to-onset for AEs of altered sensorium was approximately one day and the median duration was 15 days. A comparison of the altered sensorium AEs between patients who took efavirenz in the morning (n=27) and those who took it at bedtime (n=404) indicated that the severity and duration of the symptoms appeared to be less with bedtime dosing. A comparison of altered sensorium AEs with daily doses of efavirenz 600 mg, 400 mg and 200 mg indicated that the AE was higher in the 400 mg and 600 mg efavirenz dose groups than in the 200 mg dose group. Rashes were usually of mild to moderate severity. Onset was usually within the first 2 weeks of dosing; the estimated median duration for rash was approximately 2 weeks. The frequency and severity of rash appeared to be independent of the dose of efavirenz.

DISSOLUTION RATE METHOD AND SPECIFICATIONS FOR EFAVIRENZ 50 MG, 100 MG AND 200 MG CAPSULES

Efavirenz capsules are to be marketed in 50 mg, 100 mg, and 200 mg strengths. All strengths of the proposed commercial formulation for efavirenz contain an identical powder blend. Efavirenz is a hydrophobic compound with very low solubility in water (approximately 10 µg/ml), poor dispersability and high permeability (40 x 10^{-6} cm/sec).

The following dissolution method and specifications were agreed upon by the applicant and the FDA:
(b)(4)---

Dissolution Specification: (b)(4)--------------------

(b)(4)--

BIOANALYTICAL METHOD TO MEASURE EFAVIRENZ IN PLASMA

(b)(4)---(b)(4)-- --- The method was sensitive and specific for efavirenz. The specificity of the assay was confirmed by assaying blank human plasma and predose collections of subjects' plasma No endogenous(b)(4)------------------encountered. Linearity was established over the concentration ranges ------------------------- The accuracy and precision of the method were determined by replicate analyses (n=5) of human plasma at 4 concentrations. The accuracy as determined by percent differenc(b)(4)------------------------------ and the intraday precision as determined by percent CV ranged from----------------- Good reproducibility of the method was indicated by the low day to day %CV (interday precision) which ranged(b)(4)---------------- (b)(4)---------------------------------mined by comparing(b)(4)--------------------- --standards. Recovery of efavirenz and internal standard was gre------------------

PHASE IV COMMITMENTS

(b) (4)--

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CONCLUSIONS

The applicant has provided adequate information to permit the evaluation of the pharmacokinetics of efavirenz in healthy volunteers and HIV infected patients. The proposed dosing regimen is 600 mg once daily. The clinical trials were conducted using 50 mg, 100 mg or 200 mg capsules; the three dose strengths were directly proportional to one another. The clinical trial formulation was found to be bioequivalent to the commercial formulation. Based on the results from the studies conducted by the applicant, instructions regarding food consumption, timing of dosing, dosing in the pediatric population and concomitant medications are contained in the label. The applicant is (b)(4)-- -- -----------

RECOMMENDATION

The pharmacokinetic studies provided in NDA 20-972 (efavirenz capsules) submitted to the Division of Antiviral Drug Products to fulfil section 320 of the code of federal regulations (21 CFR) provide an understanding of the pharmacokinetics of efavirenz in adults and children. The information on the pharmacokinetics of efavirenz (Sustiva®) provided is adequate to support approval.

LABEL

A copy of the label is on file in the Division of Pharmaceutical Evaluation III.

OCPB BRIEFING DAY: September 8, 1998

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